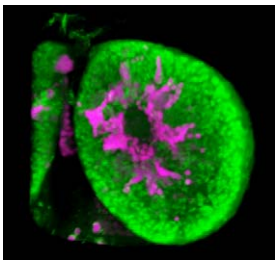
In our Select pages, we highlight exciting themes that emerge from our review of the recent literature on a particular topic. In this issue's Cell Biology Select, we discuss a cluster of recent papers that explore the delicate balance between cell polarity and proliferation and the molecular interplay between two sorts of cellular polarity, apical-basolateral and planar.

Polarity Determinants Control Neural Stem Cell Proliferation



Overexpression of membrane-targeted aPKC by fruit fly neuroblasts results in an increased number of neuroblasts at the expense of neurons due to increased self-renewal. In this brain lobe from a fruit fly larva overexpressing cortical aPKC, there are thousands of neuroblasts (green) instead of the usual number (about 100) and few differentiated neurons (magenta). (Courtesy of Cheng-Yu Lee.)

Neuroblasts of the fruit fly *Drosophila* share several key features with embryonic stem cells. When neuroblasts divide asymmetrically, they generate another neuroblast (capable of self-renewal) and a differentiated ganglion mother cell. Lee et al. now show that proteins involved in cell polarity are important for the process of neuroblast self-renewal. The investigators studied larval flies carrying mutations in two regulators of polarity: the tumor suppressor lethal giant larvae (Lgl) and an apical membrane protein called partner of inscuteable (Pins). They found that flies with mutations in *pins* produced few neuroblasts, whereas both *lgl* mutant flies and *lgl pins* double mutants produced a large number of neuroblasts at the expense of neurons, favoring self-renewal over differentiation. Based on the localization of several polarity markers in both the single and double larval fly mutants, the authors conclude that both Lgl and Pins are important for the localization of the atypical protein kinase C (aPKC) in the apical region of fly neuroblasts. There was a reduced number of neuroblasts in flies lacking *aPKC*, whereas elevated expression of cortical aPKC resulted in an increased number of neuroblasts (see the figure). The authors show that the apical localization of aPKC and its kinase activity are crucial for self-renewal, and that Lgl is able to block aPKC localization and function. They propose a model in which reciprocal inhibition by Lgl and aPKC restricts the activities of these proteins to the basolateral and apical surface, respectively, of larval fly neuroblasts. The next step will be to determine the molecules downstream of aPKC that dictate self-renewal and whether the Lee et al. model can be extended to mammalian neural stem cells.

C.-Y. Lee et al. (2005). Published online December 14, 2005. 10.1039/nature04299.

Alterations in Polarity Cause Tumor Growth

Mutations in proteins important for neuroblast polarity such as Discs large, Lgl, and Scribble cause hyperproliferation in the neural and epidermal tissues of *Drosophila.* Caussinus and Gonzalez examine the relationship between the loss of polarity in neuroblasts and the development of cancer. Brain tissue from fly larvae with individual mutations in key genes controlling asymmetric cell division—such as *aPKC* and *pins* (also called *raps*)—and in key genes specifying the cell fate of ganglion mother cells—such as *mira*, *pros*, or *numb*—were transplanted into the gut of adult flies. Larval brain tissue transplants containing neuroblasts with mutations in *Raps*, *numb*, *mira*, or *pros* (but not *aPKC*) grew to 100 times their original size. Ten to twenty percent of the flies developed tumors from the transplanted larval brain tissue. Transplantation of this tumor tissue to new locations spurred the development of new tumors. The tumors exhibited various karyotypic defects as well as an irregular number of misshapen centrosomes, a phenotype reminiscent of genomic instability in mammalian carcinomas. These findings suggest that loss of cellular polarity can lead to aberrant cell proliferation and to defects associated with cancer, such as genomic instability. Further analysis of the transplanted larval brain tissue from these fly mutants may provide important insights into tumor formation and progression.

E. Caussinus and C. Gonzalez (2005). Nat. Genet. 37, 1125–1129. Published online September 4, 2005. 10.1038/ng1632.

Endocytosis Meets Polarity and Proliferation

Another recent study strengthens the link between polarity and tumorigenesis. In a genetic screen of *Drosophila* to pinpoint factors involved in the maintenance of epithelial cell polarity, Lu and Bilder identified the *avalanche* (*avl*) gene encoding a syntaxin, a protein required for vesicle fusion during protein trafficking. In fruit fly epithelial cells, Avl preferentially colocalizes with early endosomes, implicating this syntaxin in endocytosis but not exocytosis (which has been linked to the maintenance of cell polarity). In *avl* fly mutants, apical proteins become misdirected to the basolateral surfaces of epithelial cells. In fly eye discs, *avl* mutations also lead to hyperproliferation, resulting in tumor-like growths. Intriguingly, the protein Crumbs, a determinant of apical polarity, is not degraded but rather accumulates in *avl* mutant flies. Remarkably, overexpression of Crumbs was sufficient to induce hyperproliferation, suggesting that alterations in polarity might underlie tumor formation in *avl* mutants. In support of this notion, reducing Crumbs

activity suppressed the *avl* mutant phenotype. Thus, determinants of polarity must be regulated correctly to maintain appropriate cell architecture and proliferation. This study indicates that endocytosis is required to maintain the correct apical localization of Crumbs. Together with the Lee et al. and Caussinus and Gonzalez studies, these results suggest that precise regulation of cellular polarity is essential for the control of cell proliferation, and that perturbing this polarity may lead to hyperproliferation and tumor formation.
H. Lu and D. Bilder (2005). Nat. Cell Biol. Published online October 30, 2005. 10.1038/ncb1324.

A Bacterial Protein with Tumorigenic Tendencies

The gut pathogen *Helicobacter pylori* provides yet another link between loss of cell polarity and cancer. *H. pylori* is the causative agent of gastritis, peptic ulcers, and in some individuals gastric cancer (see Essay, page 975 of this issue). *H. pylori* injects effector proteins, such as CagA, into gastric epithelial cells of the host, altering cellular morphology and promoting infection. As Bagnoli et al. now show, cultured epithelial cell monolayers overexpressing CagA lose their apical-basolateral (A/B) orientation, exhibit a reduced apical surface area, and show mislocalization of ZO-1 (a tight junction protein) to the basolateral membrane. This results in loss of adhesion between neighboring epithelial cells. Phosphorylation of CagA and altered CagA-induced matrix metalloprotease activity enables these epithelial cells to degrade basement membranes and to undergo migration, characteristics indicative of an invasive phenotype. Given studies showing a link between cell polarity and tumor formation and the Bagnoli et al. finding of changes in A/B polarity in epithelial cells overexpressing CagA, the next step will be to analyze proteins determining polarity in these cells. It also remains to be seen whether the acquisition of an invasive phenotype by epithelial cells that overexpress CagA accurately recapitulates the events leading to gastric cancer in *H. pylori*-infected individuals.
*F. Bagnoli et al. (2005). Proc. Natl. Acad. Sci. USA **102**, 16339–16344. Published online October 28, 2005. 10.1073/pnas.0502598102.*

Where A/B Polarity and Planar Cell Polarity Intersect

Cells possess both intrinsic polarity as well as polarity induced by the extracellular environment. Epithelial cells exhibit apical-basolateral (A/B) polarity that is established through asymmetric cell division. In addition, sheets of epithelial cells can become polarized in a direction that is perpendicular to the A/B axis to create planar cell polarity (PCP), which is important for developmental processes such as gastrulation in vertebrates. Epithelial cell A/B polarity and PCP were thought to be independent processes. However, recent studies including that by Dollar et al. point to an interplay between the molecules that establish these two sorts of polarity. Working in the embryonic ectoderm of the frog *Xenopus*, Dollar and colleagues show that the Dishevelled (Dsh) protein, a mediator of Wnt signaling that is important for PCP, regulates the subcellular localization and stability of Lgl, a protein that contributes to A/B polarity. Thus, Dsh provides a molecular link between A/B polarity and PCP. The interaction between these two polarity proteins is not unique to *Xenopus* embryos, however, because Dsh is also important for Lgl localization in the follicular epithelium of *Drosophila* (although whether Dsh affected Lgl stability was not reported). As Dsh acts downstream of the Wnt receptor frizzled (Fz), the authors investigated a possible connection between Lgl and Fz and found that Fz8 overexpression interfered with the localization of Lgl to membranes. By controlling the localization of Lgl, Dsh may define the regions of the cell where Lgl is active; alternatively, the interaction between Dsh and Lgl may be necessary to prevent the aberrant activation of other Dsh pathways in epithelia. How do other polarity protein complexes intersect with the Fz/Dsh/Lgl pathway? Understanding how the interaction between Dsh, A/B polarity molecules, and downstream Dsh signaling events are regulated will provide insights into the mechanisms that establish polarity during development and in epithelial tissues.
*G.L. Dollar et al. (2005). Nature **437**, 1376–1380. Published online October 27, 2005. 10.1038/nature04116.*

Cilia and PCP

Individuals with Bardet-Biedl syndrome (BBS) exhibit symptoms including age-related retinal dystrophy, polydactyly, and renal dysplasia. Defects in the assembly or function of cilia are thought to be responsible for this disease phenotype. Now Ross et al. reveal a connection between BBS and PCP. They show that mice deficient in either of two of the eight genes associated with BBS, *Bbs4* and *Mkks*, exhibit a phenotype reminiscent of mice with defects in PCP, including abnormalities in the stereocilia of the outer hair cells of the inner ear. Mice carrying mutations in both a BBS gene (*Mkks* or *Bbs1*) and a PCP gene (*Ltap*, encoding the membrane protein Vangl2) exhibit a more pronounced phenotype implicating proteins important for PCP in the assembly or function of cilia. Intriguingly, the PCP protein Vangl2 is found in several regions of cilia including the axoneme and basal bodies. It will be interesting to determine whether PCP proteins like Vangl2 are found in the centrosomes, cellular organelles related to basal bodies that are important for microtubule organization in the cell.
*A.J. Ross et al. (2005). Nat. Genet. **37**, 1135–1140. Published online September 18, 2005. 10.1038/ng1644.*

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